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Response inhibition and its relation to multidimensional impulsivity

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ABSTRACT

Impulsivity is a multidimensional construct that has been suggested as a vulnerability factor for several psychiatric disorders, especially addiction disorders. Poor response inhibition may constitute one facet of impulsivity. Trait impulsivity can be assessed by self-report questionnaires such as the widely used Barratt Impulsiveness Scale (BIS-11). However, regarding the multidimensionality of impulsivity different concepts have been proposed, in particular the UPPS self-report questionnaire ('Urgency', 'Lack of Premeditation', 'Lack of Perseverance', 'Sensation Seeking') that is based on a factor analytic approach. The question as to which aspects of trait impulsivity map on individual differences of the behavioral and neural correlates of response inhibition so far remains unclear.

In the present study, we investigated 52 healthy individuals that scored either very high or low on the BIS-11 and underwent a reward-modulated Stop-signal task during fMRI. Neither behavioral nor neural differences were observed with respect to high- and low-BIS groups. In contrast, UPPS subdomain *Urgency* best explained inter-individual variability in SSRT scores and was further negatively correlated to right IFG/aI activation in 'Stop > Go' trials — a key region for response inhibition. Successful response inhibition in rewarded compared to nonrewarded stop trials yielded ventral striatal (VS) activation which might represent a feedback signal. Interestingly, only participants with low *Urgency* scores were able to use this VS feedback signal for better response inhibition.

Our findings indicate that the relationship of impulsivity and response inhibition has to be treated carefully. We propose *Urgency* as an important subdomain that might be linked to response inhibition as well as to the use of reward-based neural signals. Based on the present results, further studies examining the influence of impulsivity on psychiatric disorders should take into account *Urgency* as an important modulator of behavioral adaptation.

Introduction

Impulsivity is a multidimensional construct and has been suggested as a potential endophenotype for several psychiatric disorders such as substance use disorder (Robbins et al., 2012). Poor response inhibition has been suggested as one facet of impulsivity. However, there are conflicting findings as to which aspects of trait impulsivity can directly be linked to response inhibition (Dick et al., 2011).

Response inhibition — the ability to withhold an inappropriate response — is one of the most important executive functions and is closely related to concepts of self-regulation and goal-directed behavior (Bari and Robbins, 2013). Response inhibition can be measured using a Stop-signal task, which requires individuals to rapidly suppress an ongoing, well-established response whenever a certain cue is suddenly presented. According to the horse-race model (Logan, 1984) the Stop-signal reaction time (SSRT) is an estimate of the time that an individual needs to withhold an ongoing response. Response inhibition as operationalized with such a Stop-signal Task is moderated by a network of cortical and sub-cortical regions, which suppresses stimulus-evoked behavior. Within this network the right inferior frontal gyrus (IFG) has

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been proposed as crucial structure for response inhibition (Aron et al., 2003).

Trait impulsivity can be assessed with self-report questionnaires like the Barratt Impulsiveness Scale (BIS-11, Patton et al., 1995), which is one of the most commonly used psychometric instruments.

There is good evidence for both higher trait impulsivity and impaired response inhibition in various neuropsychiatric disorders (Verdejo-García et al., 2008). On the other hand, in healthy controls there are conflicting results regarding the relationship between self-report impulsivity measures and experimentally operationalized response inhibition (Lijffijt et al., 2004; Logan et al., 1997). On the behavioral level, in a large sample of 504 healthy individuals prepotent response inhibition (construct derived from antisaccade, Stroop, Stop-signal, and Go/No-Go tasks) was only explained to a limited extent (only 12% of variance) by psychometrically assessed impulsivity (measured with the BIS-11, Aichert et al., 2012). On the neural level, previous imaging studies revealed heterogeneous findings regarding the association between trait impulsivity and neural activation during response inhibition. Farr et al. (2012) investigated 92 healthy subjects with a Stop-signal task and found that activation for 'stop versus go' trials in the mPFC and right anterior dorsal insula correlated negatively with trait impulsivity (especially the motor subscore of the BIS-11). In a Go/No-Go task, a negative correlation with the BIS-11 and the superior frontal gyrus was observed (Horn et al., 2003). Another study found that only the middle frontal gyrus correlated negatively with the BIS-11 motor subscale in a Go/No-Go task (Asahi et al., 2004). The heterogeneity of previous results with respect to brain regions associated with trait impulsivity during inhibition tasks may be due to the use of rather coarse self-report measures of impulsivity which do not adequately account for the different subdimensions of impulsivity.

Regarding trait impulsivity, different concepts have been proposed and impulsivity can be split up into different components. Using a factor-analytic approach, four different subdomains of impulsivity as a personality trait have been identified (Whiteside and Lynam, 2001): 1) *Urgency*: inability to inhibit action impulses especially in a negative motivational state despite long-term consequences; 2) *Premeditation*: inability to anticipate the consequences of one's actions; 3) *Perseverance*: inability to continue with boring or difficult tasks and (4) *Sensation seeking*: tendency to seek novel situations.

The subdomain *Urgency* is supposed to be related to behavioral impulsivity measures as inhibition of prepotent responses (for a meta-analysis see Cyders and Coskunpinar, 2011). This points towards the so far untested hypothesis that *Urgency* may explain individual variability in the behavioral and neural correlates of a Stop-signal task.

Trait impulsivity has been linked to alterations during reward processing: especially high impulsive individuals have been proposed to be more sensitive to immediate rewards and thus show stronger delay discounting (Ainslie, 1975; Hoogman et al., 2011; Hariri et al., 2006). Activation during reward processing has been shown to be related to trait impulsivity measures (Forbes et al., 2009). In a recent review, Plichta and Scheres (2014) postulate a positive relationship of trait impulsivity and ventral striatum(VS) BOLD signal during reward processing and anticipation in healthy participants.

The influence of reward effects on response inhibition has received limited attention so far. One behavioral study found a beneficial effect of reward on response inhibition in healthy students (Boehler et al., 2012, see also Scheres et al., 2001, and Sinopoli et al., 2011). A subsequent fMRI study demonstrated elevated activation of the so-called 'inhibition network' when comparing reward- to nonreward-associated trials (Boehler et al., 2014). Based on the finding of altered reward processing in impulsive individuals (Plichta and Scheres, 2014) we asked how the relationship between trait impulsivity and response inhibition is modulated by reward. Here we investigated the influence of self-report trait impulsivity measures on response inhibition using a reward-modulated Stop-signal task (Boehler et al., 2012). A sample of high compared to low impulsive healthy individuals was preselected from the extreme ends of self-report trait impulsivity (for a similar approach studying trait aggression compare Pawliczek et al., 2013).

Given the mixed findings, we probed if high impulsive individuals show poorer response inhibition (longer SSRT) associated with lower activation of the cortical inhibition network especially the right inferior frontal gyrus (IFG). Further, we probed the relationship of multiple subdimensions of impulsivity and the behavioral and neural correlates of response inhibition which we expected to find in the ventral striatum and the prefrontal cortex, especially the anterior cingulate cortex (Boehler et al., 2014; Scheres et al., 2007; Christakou et al., 2011). In addition, we tested how different dimensions of impulsivity interact with reward and its influence on response inhibition.

Methods

Participants

From a total sample of 452 participants who completed the Barratt Impulsiveness Scale-11 (Patton et al., 1995) we selected 52 right-handed high or low scoring individuals from the upper and lower end of the range (for a distribution of the BIS-11 scores in our sample, see supplement Figure S1B). The mean BIS-score for each group fulfilled criteria for classifying subjects as high or low impulsive (Stanford et al., 2009). Subjects were matched for age and gender and screened for psychiatric disorders using the SCID-IV interview. Based on this screening, one participant was excluded because of a recent episode of major depressive disorder. A further two subjects were excluded due to malfunctioning of the buttons during fMRI scanning, leading to a total sample of 49 participants.

All participants were paid on an hourly basis and gave written informed consent to participate in the study. The study was approved by the local ethics committee. In order to compare the multiple dimensions of impulsivity, all participants additionally filled out the German version of the UPPS self-report questionnaire containing the subdimensions 'urgency', 'lack of perseverance', 'lack of premeditation' and 'sensation seeking' (Whiteside and Lynam, 2001), the NEO-FFI-30 (Körner et al., 2008), and the Sensation Seeking Scale (SSS, Zuckerman et al., 1978). To assess verbal intelligence, working memory and cognitive speed, participants underwent neuropsychological testing including a German version of the vocabulary test (Schmidt and Metzler, 1992) and the Digit Span(taken from a German version of the WAIS-III, Von Aster, Neubauer & Horn, 2006).

Paradigm

Participants performed a modified staircase-adapted Stop-signal task (Logan, 1994, see Fig. 1). In this task, subjects are instructed to respond by button press as fast as possible to a Go-signal. In a minority (33%) of trials the Go-signal is subsequently replaced by a Stop-signal prompting the subjects to withhold their response. As Go-trials form the majority of trials and the Stop-signal emerges suddenly after the Go-signal, Stop-trials force participants to cancel an already initiated prepotent response.

In order to achieve a stopping rate of approximately 50%, we introduced a staircase procedure that varied the Stop-signal-delay (SSD) after each Stop-trial. After an unsuccessful Stop-trial (US) 34 ms were subtracted from the individual SSD making it easier for the participants to inhibit their response. Accordingly, a successful Stop-trial (SS) led to an extended SSD by 34 ms, thus making it more difficult for the participants to withhold their response. Participants yielded a minimum and maximum SSD of 67 ms and 533 ms respectively. This procedure results in around 50% successful Stop-trials and enabled the computation of the Stop-signal reaction time (SSRT) as described in the following section. Go-trials were presented as traffic light symbols pointing either to the right or to the left. Participants were instructed to press the button corresponding to the direction of the symbol using their thumbs. In each